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(FILE 'HOME' ENTERED AT 16:56:12 ON 30 MAR 2004)

FILE 'MEDLINE' ENTERED AT 16:56:19 ON 30 MAR 2004

L1	66960	S	RETINO?
L2	2093	S	L1 AND RAR
L3	332	S	L2 AND ANTAGONIST?
L4	8	S	L3 AND REVIEW?
L5	3513	S	L1 AND ANTAGONIST?
L6	123	S	L5 AND REVIEW?
L7	19	S	L6 AND STRUCTURE
L8	10	S	L6 AND (STRUCTURE ACTIVITY)
L9	7	S	L8 NOT L4
L10	807	S	RAR AND RXR
L11	155	S	L10 AND ANTAGONIST?
L12	5	S	L11 AND REVIEW?
L13	0	S	L12 NOT L4
L14	26	S	L3 AND (STRUCTURE ACTIVITY)
L15	26	S	L14 NOT L9

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SESSION RESUMED IN FILE 'MEDLINE' AT 17:00:53 ON 30 MAR 2004
FILE 'MEDLINE' ENTERED AT 17:00:53 ON 30 MAR 2004
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.38	0.59

=> s retino?
L1 66960 RETINO?

=> s l1 and RAR
2465 RAR
L2 2093 L1 AND RAR

=> s l2 and antagonist?
459810 ANTAGONIST?
L3 332 L2 AND ANTAGONIST?

=> s l3 and review?
531409 REVIEW?
L4 8 L3 AND REVIEW?

=> d 1-8 bib abs

L4 ANSWER 1 OF 8 MEDLINE on STN
AN 2004058072 IN-PROCESS
DN PubMed ID: 14758758
TI Synthetic applications of palladium-catalyzed hydroarylation and related systems.
AU Mitchell David; Yu Hannah
CS Eli Lilly & Company, Lilly Research Laboratories, Global Chemical Process Research and Development, Indianapolis, IN 46285, USA.. dmit@lilly.com
SO Current opinion in drug discovery & development, (2003 Nov) 6 (6) 876-83. Journal code: 100887519. ISSN: 1367-6733.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20040205
Last Updated on STN: 20040205
AB Synthetic organic chemists have recognized the hydroarylation of alkynes and alkenes as a versatile methodology. In the first part of this **review**, the regio- and stereochemistry of the hydroarylation of alkynes and the synthetic applications of this reaction in the synthesis of antiviral agents and steroid derivatives will be discussed. In the second part, applications of the hydroarylation of alkenes in the syntheses of epibatidine analogs, argemonine, **retinoid** X receptor (RXR), **retinoic** acid receptor (**RAR**) modulators and neurokinin (NK) receptor NK1 **antagonists** will be discussed. Emphasis will be placed on the application of Pd-catalyzed hydroarylation to the synthesis of biologically active compounds.

L4 ANSWER 2 OF 8 MEDLINE on STN
AN 2002211787 MEDLINE
DN PubMed ID: 11945128
TI Discovery and design of **retinoic** acid receptor and **retinoid** X receptor class- and subtype-selective synthetic analogs of all-trans-**retinoic** acid and 9-cis-**retinoic** acid.
AU Dawson Marcia I; Zhang Xiao-kun
CS Department of Medicinal Chemistry, Molecular Medicine Research Institute, Mountain View, La Jolla, CA 94043, USA.. mdawson@mmrx.org
NC CA51993 (NCI)
SO Current medicinal chemistry, (2002 Mar) 9 (6) 623-37. Ref: 121 Journal code: 9440157. ISSN: 0929-8673.
CY Netherlands
DT Historical
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200307
ED Entered STN: 20020412
Last Updated on STN: 20021211
Entered Medline: 20030725
AB This **review** presents a historical overview of the discoveries of **retinoic** acid receptor (**RAR**) and **retinoid** X receptor (RXR) class- and subtype-selective synthetic **retinoids**. These synthetic **retinoids** are conformationally restricted by

having aromatic rings in place of the tetraene bond systems of all-trans- and 9-cis-**retinoic** acids. Events leading to the design and synthesis of such **retinoid** transcriptional agonists as **RAR** subtype beta,gamma-selective 6-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2-naph-thalenecarboxylic acid (TTNN), the RARgamma-selective Z-oxime of 6-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenylcarbonyl)-2-naphthalenecarboxylic acid (SR11254), **RAR** -selective 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-anthracenyl) benzoic acid (TTAB), RXR-selective 4-[1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-cyclopropyl] benzoic acid (SR11246), RXR-selective 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)-2-methylpropenyl]benzoic acid (SR11345), and RARgamma-selective **retinoid** transcriptional **antagonist** 2-(6-carboxy-2-naphthalenyl)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1,3-dithiolane (SR11253) are described.

L4 ANSWER 3 OF 8 MEDLINE on STN
AN 2002211330 MEDLINE
DN PubMed ID: 11945126
TI Novel synthetic **retinoids** and separation of the pleiotropic **retinoidal** activities.
AU Kagechika Hiroyuki
CS Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, Tokyo 113-0033, Japan.. kage@mol.f.u-tokyo.ac.jp
SO Current medicinal chemistry, (2002 Mar) 9 (5) 591-608. Ref: 81
Journal code: 9440157. ISSN: 0929-8673.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200304
ED Entered STN: 20020412
Last Updated on STN: 20030409
Entered Medline: 20030408
AB **Retinoids**, all-trans-**retinoic** acid (1a) and its analogs, act as specific modulators of cellular differentiation and proliferation, through binding to and activating specific nuclear receptors, **retinoic** acid receptors (RARs) and **retinoid** X receptors (RXRs). **Retinoids** have chemotherapeutic roles in dermatology and oncology, but their usefulness is restricted by the high toxicity of **retinoic** acid and its hydrophobic analogs. We have developed various **retinoidal** benzoic acid derivatives, and named them **retinobenzoic** acids. Among them, aromatic amides such as Am80 (7) and Am580 (8) have superior pharmacological characteristics, including **RAR** subtype selectivity. Structural modification based on the ligand superfamily concept afforded several types of **RAR antagonists**, benzimidazole derivatives, BIPh (41) and BIBn (42), and dibenzodiazepine derivatives, LE135 (46) and LE540 (47). LE135 (46) is a unique **antagonist** with RARbeta-selectivity. During investigations on the structure-activity relationships of **retinobenzoic** acids, several **retinoid** synergists (RXRs agonists), such as HX600 (49), DA113 (55h) and TZ335 (57), have been found. These compounds are expected to modulate other nuclear receptors which form heterodimers with RXRs, besides **retinoids**. Further, we found some RXRs **antagonists**, HX531 (60) and HX603 (61), which inhibit the activation of both RXR homodimers and RXR **RAR** heterodimers. In this **review**, we describe our investigations on these structurally and biologically unique **retinoids** and **retinoid**-regulatory compounds.

L4 ANSWER 4 OF 8 MEDLINE on STN
AN 2001455630 MEDLINE
DN PubMed ID: 11501968
TI ATRA(ouble) in the treatment of acute promyelocytic leukemia.
AU Ozpolat B; Lopez-Berestein G; Mehta K
CS Department of Bioimmunotherapy, The University of Texas, MD Anderson Cancer Center, Houston 77030, USA.
NC R-00923
SO Journal of biological regulators and homeostatic agents, (2001 Apr-Jun) 15 (2) 107-22. Ref: 172
Journal code: 8809253. ISSN: 0393-974X.
CY Italy
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English

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FS Priority Journals
EM 200202
ED Entered STN: 20010815
Last Updated on STN: 20020209
Entered Medline: 20020208
AB Acute promyelocytic leukemia (APL) is a unique disease that responds to differentiation-inducing effects of all-trans-**retinoic** acid (ATRA). ATRA induces complete clinical remissions (CRs) in most patients and now constitutes a standard therapy in patients with APL. However, CRs induced by ATRA are usually brief, and resistance to the therapy rapidly develops, leading to relapses in almost every patient; thus limiting the use of ATRA as a single agent. On the basis of clinical and in vitro studies, the following mechanisms have been proposed to explain ATRA resistance: 1) induction of accelerated metabolism of ATRA, 2) increased expression of cellular **retinoic** acid-binding proteins (CRABPs), 3) constitutive degradation of PML-**RAR** alpha, 4) point mutations in the ligand-binding domain of **RAR** alpha of PML-**RAR** alpha, 5) P-glycoprotein expression, 6) transcriptional repression by histone deacetylase activity, 7) isoforms of PML-**RAR** alpha, 8) persistent telomerase activity, and 9) expression of type II transglutaminase. In this **review**, we discuss the evidence provided in support of each mechanism, the mechanism's possible impact on the outcome of APL, and the newer approaches that are being employed to overcome ATRA resistance.

L4 ANSWER 5 OF 8 MEDLINE on STN
AN 2001194813 MEDLINE
DN PubMed ID: 11242632
TI Molecule targeted therapy for hematological malignancies.
AU Naoe T
CS Dept. of Infectious Diseases, Nagoya University School of Medicine.
SO Gan to kagaku ryoho. Cancer & chemotherapy, (2001 Feb) 28 (2) 131-4. Ref: 7
Journal code: 7810034. ISSN: 0385-0684.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LA Japanese
FS Priority Journals
EM 200104
ED Entered STN: 20010410
Last Updated on STN: 20010410
Entered Medline: 20010405
AB Over the past 20 years, there has been a marked increase in our knowledge of the molecular mechanisms of human hematological malignancies. The development of mechanism-based therapy is expected to extend the frontiers of chemotherapy. All-trans **retinoic** acid (ATRA) therapy for acute promyelocytic leukemia (APL), initially established as differentiation therapy, has been recognized to target PML-**RAR** alpha protein, an APL-specific chimeric transcriptional factor, and to modulate the function. Recently, encouraging results have emerged in the treatment of chronic myeloid leukemia with a tyrosine-kinase inhibitor. In addition to the oncoprotein-targeted therapy, the clinical effectiveness of humanized monoclonal antibodies to differentiation antigens has been recognized. Molecule-targeted therapy is **reviewed** herein.

L4 ANSWER 6 OF 8 MEDLINE on STN
AN 2000291536 MEDLINE
DN PubMed ID: 10828316
TI Recent developments in receptor-selective **retinoids**.
AU Nagpal S; Chandraratna R A
CS Retinoid Research, Department of Biology and Chemistry, Allergan Inc., Irvine, CA-92713, USA.
SO Current pharmaceutical design, (2000 Jun) 6 (9) 919-31. Ref: 71
Journal code: 9602487. ISSN: 1381-6128.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200007
ED Entered STN: 20000811
Last Updated on STN: 20000811
Entered Medline: 20000731
AB Natural (all trans-**retinoic** acid, RA) and synthetic

retinoids exhibit potent anti-proliferative, normalization of differentiation and anti-inflammatory activities which appear to account for their therapeutic effects in acne, psoriasis, photoaging, precancerous lesions and established cancers. Although RA has shown considerable promise in dermatologic indications, certain side effects have restricted its use as a choice of agent for chronic administration. Systematic synthesis of receptor-selective **retinoids** has resulted in two topical drugs, Tazorac/Zorac (tazarotene) and Differin (adapalene). Tazorac is indicated for psoriasis and acne and Differin gel for the treatment of acne. These drugs bind to the **retinoic** acid receptor (**RAR**) family members. Various **RAR** subtype-specific and function-selective **retinoids** have been synthesized. These **retinoids**, which are in various stages of pre-clinical development for the treatment of cancers, psoriasis and as an antidote to Accutane-mediated mucocutaneous toxicity, will also be discussed in this **review.** Discovery of another **retinoid** receptor, **retinoid** X receptor (RXR), revealed that RXR-specific **retinoids** already existed in **retinoid** chemical libraries. Structure activity relationship studies based upon binding and transactivation assays led to the synthesis of RXR-specific ligands with high affinities for RXR subtypes. These compounds were found to be effective in the treatment of hyperglycemia in animal models of type II diabetes. The discovery of novel **retinoids** along with an increased understanding of the biological functions and mechanisms of action of **retinoid** receptors are likely to result in improved treatments for existing responsive indications and identification of new **retinoid** therapeutic targets.

L4 ANSWER 7 OF 8 MEDLINE on STN
AN 2000105744 MEDLINE
DN PubMed ID: 10637371
TI Therapeutic applications for ligands of **retinoid** receptors.
AU Thacher S M; Vasudevan J; Chandraratna R A
CS Retinoid Research, Departments of Biology and Chemistry, Allergan Inc., Irvine, California 92623, USA.
SO Current pharmaceutical design, (2000 Jan) 6 (1) 25-58. Ref: 216
Journal code: 9602487. ISSN: 1381-6128.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200003
ED Entered STN: 20000327
Last Updated on STN: 20000327
Entered Medline: 20000315
AB Synthetic **retinoids**, ligands for the **RAR** and RXR members of the steroid/thyroid superfamily of nuclear hormone receptors, are used for the treatment of psoriasis, acne, photoaging and cancer. **Retinoid** mechanisms of action for these conditions largely involve effects on epithelial differentiation and modulation of inflammation with some impact on the immune system. **Retinoid** medicinal chemistry in recent years has identified ligands highly specific for one of the three **RAR** subtypes (**RAR**-alpha) and for the RXR family of receptors, as well as **antagonists** for the RARs, RARalpha and the RXRs. Structure-activity relationships among the novel **retinoid** classes are **reviewed** along with potential therapeutic activities and side effects. **RAR**-alpha specific **retinoids** inhibit cancer cell growth but lack other **retinoid** toxicities, including skin irritation now ascribed to **RAR**-gama. RXR-specific **retinoids** lower blood glucose in animal models of type 2 diabetes albeit with a potential for mild hypothyroidism. Function-selective **retinoids**, especially a class of **RAR antagonists** called inverse agonists, have unexpected gene regulatory activity. Given the diverse properties and tissue distributions of the **retinoid** receptors, synthesis of additional classes of receptor-specific and function-selective ligands has the potential to produce novel therapeutic applications.

L4 ANSWER 8 OF 8 MEDLINE on STN
AN 96119553 MEDLINE
DN PubMed ID: 8589015
TI Therapy-related acute promyelocytic leukemia with t(15;17) (q22;q12) following chemotherapy with drugs targeting DNA topoisomerase II. A report of two cases and a **review** of the literature.
CM Comment in: Ann Oncol. 1995 Oct;6(8):751-3. PubMed ID: 8589010
AU Hoffmann L; Moller P; Pedersen-Bjergaard J; Waage A; Pedersen M; Hirsch F

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CS Laboratory for Cancer Genetics and Cytogenetics, Finsen Center, Rigshospitalet, Copenhagen, Denmark.

SO Annals of oncology : official journal of the European Society for Medical Oncology / ESMO, (1995 Oct) 6 (8) 781-8. Ref: 32
Journal code: 9007735. ISSN: 0923-7534.

CY Netherlands

DT (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW OF REPORTED CASES)

LA English

FS Priority Journals

EM 199603

ED Entered STN: 19960404
Last Updated on STN: 19960404
Entered Medline: 19960327

AB BACKGROUND: The development of therapy-related acute myeloid leukemia (t-AML) with balanced translocations to chromosome bands 11q23 and 21q22 has recently been significantly related to previous treatment with several cytostatic drugs poisoning DNA topoisomerase II. A similar association was suspected for other balanced chromosomal aberrations such as the t(15;17) characteristic of acute promyelocytic leukemia (APL). PATIENTS AND METHODS: Two cases of acute promyelocytic leukemia were observed following treatment for seminoma with etoposide, cisplatin, and bleomycin and treatment for breast cancer with 4-epi-doxorubicin and subsequent cyclophosphamide, methotrexate, and 5-fluorouracil followed by radiotherapy. Both cases presented a t(15;17) (q22;q12) and were examined for the characteristic chimeric rearrangement of the **RAR** alpha and PML genes observed in acute promyelocytic leukemia de-novo. RESULTS: In both cases the characteristic chimeric rearrangement was demonstrated. Case number 2 in addition to the t(15;17) showed an inversion of the long arm of a chromosome number 5 and a del(7)(q22) in all abnormal mitoses studied. Despite these findings the patient obtained a complete morphological and cytogenetic remission of the leukemia following treatment with all-trans-**retinoic** acid. CONCLUSIONS: Based on these two cases and a **review** of the literature it is concluded that the development of t-APL with the balanced translocation t(15;17) is related to previous treatment with cytostatic drugs targeting DNA topoisomerase II and that additional abnormalities of the long arms of chromosomes number 5 and number 7 do not interfere with the induction of remission with all-trans-**retinoic** acid.

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=> d 1-7 bib abs

L9 ANSWER 1 OF 7 MEDLINE on STN
AN 2003602134 MEDLINE
DN PubMed ID: 14683516
TI **Structure-activity** relationship of nuclear receptor-ligand interactions.
AU Greschik Holger; Moras Dino
CS Departement de Biologie et Genomique Structurales, Institut de Genetique et de Biologie Moleculaire et Cellulaire, 1 rue Laurent Fries, B.P. 10142, 67404 Illkirch, France.
SO Current topics in medicinal chemistry, (2003) 3 (14) 1573-99. Ref: 121
Journal code: 101119673. ISSN: 1568-0266.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200402
ED Entered STN: 20031220
Last Updated on STN: 20040207
Entered Medline: 20040206
AB Small molecules such as **retinoids**, steroid hormones, fatty acids, cholesterol metabolites, or xenobiotics are involved in the regulation of numerous physiological and patho-physiological processes by binding to and controlling the activity of members of the nuclear receptor (NR) superfamily of transcription factors. In addition to natural ligands, synthetic agonists or **antagonists** have been identified that in some cases specifically target NR isotypes, or elicit tissue-, signaling pathway-, or promoter-selective transcriptional responses. For these ligands the term "selective NR modulators" (SNRMs) has been introduced. Structure determination of apo- and holo-NR ligand-binding domains (LBDs)--some of them complexed to small coactivator or corepressor fragments--revealed the major principles of ligand-dependent NR action and determinants of (isotype-) selective ligand binding. These studies also stimulated the interpretation of tissue-specific effects of SNRMs on wild-type or mutant receptors. In contrast to the increasing knowledge on the **structure-activity** relationship of NRs with known SNRMs, rather basic questions remain about the regulation of orphan NRs (for which no ligands are known) or "adopted" orphan NRs (for which only recently ligands were identified). Several crystal structures of orphan NR LBDs uncovered unexpected properties, contributed to the understanding of orphan NR function, and may in the future permit the identification or design of ligands. This **review** will (i) focus on the current understanding of the **structure-activity** relationship of NR-ligand interactions, (ii) discuss recent advances in the field of "orphan" NR crystallography, and (iii) outline future challenges in NR structural biology.

L9 ANSWER 2 OF 7 MEDLINE on STN
AN 2003338917 MEDLINE
DN PubMed ID: 12871134
TI Aldose reductase inhibitors from the nature.
AU Kawanishi K; Ueda H; Moriyasu M
CS Department of Natural Medicinal Chemistry, Faculty of Pharmacy, Kobe Pharmaceutical University, Motoyamakitamachi 4-19-1, Higashinadaku, Kobe 658-8558, Japan.
SO Current medicinal chemistry, (2003 Aug) 10 (15) 1353-74. Ref: 40
Journal code: 9440157. ISSN: 0929-8673.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LA English
FS Priority Journals
EM 200403
ED Entered STN: 20030722
Last Updated on STN: 20040326
Entered Medline: 20040325
AB Aldose reductase (AR) is an NADPH dependent enzyme that catalyses the reduction of the aldehyde to the corresponding alcohols. Diabetic complications including neuropathy, nephropathy, cataracts and **retinopathy** are considerately caused by accumulation of sorbitol, which is produced from glucose by AR in polyol pathway. The aim of AR inhibitor therapy is to normalize the elevated flux of blood and sorbitol through the polyol pathway in the target tissue. A large number of inhibitors have been prepared synthetically, and some of them are used

therapeutically. However, none of them is satisfactory. From the plants, many AR inhibitors have been found, which are discussed in this **review.** By the structure based functioning of AR and its inhibitors, some will be developed promising in the treatment of diabetic complications. The main structural features of the inhibitors will be a polar head group and a hydrophobic ring system. The plants that contain the AR inhibitors may prevent from diabetic complications.

L9 ANSWER 3 OF 7 MEDLINE on STN
AN 2003298483 MEDLINE
DN PubMed ID: 12825457
TI Recent advances and new directions in the discovery and development of cyclin-dependent kinase inhibitors.
AU Fischer P M
CS Cyclacel Ltd., James Lindsay Place, Dundee, DD1 5JJ, Scotland, UK.. pfischer@cyclacel.com
SO Current opinion in drug discovery & development, (2001 Sep) 4 (5) 623-34. Ref: 101
Journal code: 100887519. ISSN: 1367-6733.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200307
ED Entered STN: 20030627
Last Updated on STN: 20030722
Entered Medline: 20030721
AB The eukaryotic cell division cycle is coordinated by cyclin-dependent protein kinases (CDKs) and cyclin subunits specific for the different phases of the cycle. These complexes phosphorylate target substrates, including the **retinoblastoma** susceptibility gene product (pRb) and related proteins. Cellular neoplastic transformations are accompanied by loss of regulation of cell cycle checkpoints, frequently through aberrant expression of CDKs and cyclins, as well as loss or mutation of their negative regulators. Consequently, one strategy in the development of mechanism-based anticancer therapeutics has been to halt malignant cellular proliferation through inhibition of the enzymatic activity of CDKs. The development of inhibitors selective for the ATP binding sites of particular protein kinases is a comparatively recent medicinal chemistry endeavor. Advances relevant to CDK inhibition are **reviewed** critically and alternative approaches to CDK inhibition, as well as applications of CDK inhibitors to therapeutic areas other than oncology, are also discussed.

L9 ANSWER 4 OF 7 MEDLINE on STN
AN 2002347318 MEDLINE
DN PubMed ID: 12090548
TI Pegvisomant. Pharmacia.
AU Goffin Vincent; Touraine Philippe
CS INSERM, Unite 344, Faculte de Medecine Necker, Paris, France.. goffin@necker.fr
SO Current opinion in investigational drugs (London, England : 2000), (2002 May) 3 (5) 752-7. Ref: 68
Journal code: 100965718. ISSN: 1472-4472.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200301
ED Entered STN: 20020702
Last Updated on STN: 20030314
Entered Medline: 20030127
AB Pegvisomant, a polyethylene glycol (PEG) derivative of human growth hormone (GH) that acts as a highly selective GH receptor **antagonist**, is under development by Pharmacia (formerly Sensus) as a potential treatment for acromegaly. By February 2001, Sensus had submitted an NDA for the treatment of acromegaly, and an approvable letter indicating outstanding issues had been received by July 2001. Pegvisomant was granted Orphan Drug status by the FDA and was designated for Priority **Review.** Pegvisomant also received Orphan Drug designation in the EU and Japan. In March 2001, additional regulatory filings were being planned for later in 2001. In October 2001, Pharmacia was preparing an NDA in Japan for the treatment of acromegaly. By September 1998, phase 1 trials of the treatment were underway for diabetic **retinopathy,**

and were planned for diabetic nephropathy in 1999. By September 1997, a phase II trial to test the effects of pegvisonant an insulin sensitivity and secretion in type II diabetes patients was underway. However, no development has been reported for these indications since the dates given. By 1994, Sensus had licensed technology for development of GH receptor **antagonists** from Genentech and Ohio University. Sensus was to pay Genentech, and Genentech was to receive equity in Sensus and royalties from the commercialization of any product resulting from the agreement. In April 2000, the company entered into a licensing agreement with Shearwater Polymers for the PEGylation of pegvisomant using Shearwater's proprietary technology, which is now used to produce the 20-kDa PEG-derivative of pegvisomant. In June 1999, Pharmacia Corp (formerly Pharmacia & Upjohn) signed an agreement to purchase 19.9% of Sensus and to potentially acquire the remainder of the company at a later date. In March 2001, Pharmacia completed its purchase of Sensus. Analysts at Merrill Lynch predicted in February 2002 that the product would be launched in 2003, with US revenues of $20 million, rising to $115 million in 2006.

L9 ANSWER 5 OF 7 MEDLINE on STN
AN 2001215845 MEDLINE
DN PubMed ID: 11249708
TI Bexarotene ligand pharmaceuticals.
AU Hurst R E
CS Department of Urology, Oklahoma University Health Sciences Center, Oklahoma City, OK 73190, USA.. robert-hurst@ouhsc.edu
SO Current opinion in investigational drugs (London, England : 2000), (2000 Dec) 1 (4) 514-23. Ref: 74
Journal code: 100965718. ISSN: 1472-4472.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200104
ED Entered STN: 20010425
Last Updated on STN: 20010425
Entered Medline: 20010419
AB Bexarotene (LGD-1069), from Ligand, was the first **retinoid** X receptor (RXR)-selective, antitumor **retinoid** to enter clinical trials. The company launched the drug for the treatment of cutaneous T-cell lymphoma (CTCL), as Targretin capsules, in the US in January 2000 [359023]. The company filed an NDA for Targretin capsules in June 1999, and for topical gel in December 1999 [329011], [349982] specifically for once-daily oral administration for the treatment of patients with early-stage CTCL who have not tolerated other therapies, patients with refractory or persistent early stage CTCL and patients with refractory advanced stage CTCL. The FDA approved Targretin capsules at the end of December 1999 for once-daily oral treatment of all stages of CTCL in patients refractory to at least one prior systemic therapy, at an initial dose of 300 mg/m2/day. After an NDA was submitted in December 1999 for Targretin gel, the drug received Priority **Review** status for use as a treatment of cutaneous lesions in patients with stage IA, IB or IIA CTCL [354836]. The FDA issued an approvable letter in June 2000, and granted marketing clearance for CTCL in the same month [370687], [372768], [372769], [373279]. Ligand had received Orphan Drug designation for this indication [329011]. At the request of the FDA, Ligand agreed to carry out certain post-approval phase IV and pharmacokinetic studies [351604]. The company filed an MAA with the EMEA for Targretin Capsules to treat lymphoma in November 1999 [348944]. The NDA for Targretin gel is based on a multicenter phase III trial that was conducted in the US, Canada, Europe and Australia involving 50 patients and a multicenter phase I/II clinical program involving 67 patients. Targretin gel was evaluated for the treatment of patients with early stage CTCL (IA-IIA) who were refractory to, intolerant to, or reached a response plateau for at least 6 months on at least two prior therapies. Efficacy results exceeded the protocol-defined response target rates; side effects were primarily limited to local skin reactions [349982]. Ligand has worldwide rights to market bexarotene capsules, and will market the drug in the US, Canada and selected European markets. In Spain, Portugal, Greece and Central and South America, Ferrer Internacional will market and distribute the drug. As of December 1999, Ligand was seeking additional distribution partners for select European and Asian markets [351604]. In January 2000, Alfa Wassermann signed an agreement with Ligand to exclusively market and distribute Targretin gel and capsules in Italy. Alfa paid US $0.75 million on signing with additional amounts up to an aggregate total of US $1.0 million on achievement of certain registration milestones, which are

expected to be met in 2000 [351882].

L9 ANSWER 6 OF 7 MEDLINE on STN
AN 2001201427 MEDLINE
DN PubMed ID: 11148374
TI [Imidazolidine/thiazolidine-acetate aldose reductase inhibitors]. Les inhibiteurs de l'aldose-reductase de structure imidazolidine/thiazolidine-acetique.
AU Fresneau P
CS Laboratoire de Chimie Therapeutique, Groupe de Pharmacochimie Moleculaire, Faculte de Pharmacie, F38700 La Tronche.
SO Annales pharmaceutiques francaises, (2000 Dec) 58 (6) 392-404. Ref: 48
Journal code: 2985176R. ISSN: 0003-4509.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA French
FS Priority Journals
EM 200104
ED Entered STN: 20010417
Last Updated on STN: 20010417
Entered Medline: 20010412
AB We studied a new family of aldose-reductase inhibitors with an imidazolidine arylmethylene and thiazolidine-acetate structure susceptible to prevent ocular, renal and vascular complications of insulin-dependent diabetes mellitus. We examined the role of the enzyme in the pathological processes involved and **reviewed** knowledge of known aldose reductase inhibitors leading to the development of the basic structure modulated to have insight into the different elements of the structure-quantitative activity relationship. Potential inhibitors are synthesized by condensation of heterocyclic rings and aldehyde aromatic rings. Their identity and structure were established by magnetic resonance spectroscopy (MRS) based on proton-carbon couplage constants and the homonuclear NOE effect. The **structure-activity** correlations were analyzed on the basis of the IC50 using a structural model and a physicAL model which showed the importance of the sulfur atom in the heterocyclic ring due to its important lipophilic contribution. Finally, a molecular modeling approach led to a provisional descriptive model of the inhibitor-enzyme interaction.

L9 ANSWER 7 OF 7 MEDLINE on STN
AN 1999114724 MEDLINE
DN PubMed ID: 9918192
TI Diabetes complications and their potential prevention: aldose reductase inhibition and other approaches.
AU Costantino L; Rastelli G; Vianello P; Cignarella G; Barlocco D
CS Dipartimento di Scienze Farmaceutiche, Modena, Italy.
SO Medicinal research reviews, (1999 Jan) 19 (1) 3-23. Ref: 153
Journal code: 8103150. ISSN: 0198-6325.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199903
ED Entered STN: 19990326
Last Updated on STN: 19990326
Entered Medline: 19990317
AB Despite recent advances both in the chemistry and molecular pharmacology of antidiabetic drugs, diabetes still remains a life-threatening disease, which tends to spread all over the world. The clinical profile of diabetic subjects is often worsened by the presence of several long-term complications, namely neuropathy, nephropathy, **retinopathy**, and cataract. Several attempts have been made to prevent or at least to delay them. The most relevant are reported in this **review**, including the development of compounds acting as aldose reductase inhibitors, anti-advanced glycation end-product drugs, free radical scavengers, vasoactive agents, essential fatty acid supplementation, and neurotropic growth factors.

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=> d 14-26 bib abs

L15 ANSWER 14 OF 26 MEDLINE on STN
AN 1998338121 MEDLINE
DN PubMed ID: 9673404
TI Antiproliferative activity and apoptosis induced by **retinoic** acid receptor-gamma selectively binding **retinoids** in neuroblastoma.
AU Meister B; Fink F M; Hittmair A; Marth C; Widschwendter M
CS Department of Pediatrics, University of Innsbruck, Austria.. b.meister@tirol.com
SO Anticancer research, (1998 May-Jun) 18 (3A) 1777-86.
Journal code: 8102988. ISSN: 0250-7005.
CY Greece
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199808
ED Entered STN: 19980820
Last Updated on STN: 19980820
Entered Medline: 19980810
AB **Retinoids** modulate several cell functions and especially inhibit the growth of tumor cells. Their biological activity is mediated by **retinoic** acid receptors (RARs), of which three subtypes (alpha, beta, gamma) have been identified. In human neuroblastoma (NB) reduced endogenous **RAR**-gamma expression was suggested to diminish the sensitivity for **retinoids**, to promote proliferation, and to contribute to the malignant phenotype. To correlate receptor selectivity with in vitro activity, we analysed the effect of six synthetic **retinoids** with selectivity for human **RAR** -alpha/beta/gamma on the human LAN-5 NB cell line and compared it with the natural compound all-trans-**retinoic** acid (ATRA). Apoptosis was determined by flow-cytometry using terminal-deoxynucleotidyl transferase to end-label DNA fragments in situ in apoptotic cells. The **antagonist** for **RAR**-beta/gamma CD2665 as well as the selective agonists for **RAR**-alpha CD336 and **RAR**-beta CD2019 were less effective in growth inhibition than ATRA. In contrast, the synthetic **RAR**-gamma selective agonists CD437 and CD2325 induced a concentration- and time-dependent antiproliferative effect, which was similar or even more pronounced than ATRA. In contrast to ATRA, the adition of CD437 and CD2325 did not induce morphological changes typical of NB cell maturation but resulted in morphological features consistent with the occurrence of programmed cell death. Flow-cytometric analysis showed that in contrast to ATRA the addition of CD 437 and CD 2325 results in progressive time-dependent increase of apoptotic cells (25.9% and 57.7% after 72 hours). In conclusion, our study demonstrates **RAR**-gamma selectively binding **retinoids** dramatically suppress NB cell growth, primarily by inducing programmed cell death rather than by cell differentiation. Since advanced or disseminated NB tumors endogenously express low levels of **RAR**-gamma and lack of apoptosis is involved in tumor progression, **RAR**-gamma selectively binding **retinoids** may be more appropriate **retinoids** for clinical trials in NB.

L15 ANSWER 15 OF 26 MEDLINE on STN
AN 97358279 MEDLINE
DN PubMed ID: 9215399
TI Effects of **retinoid** X receptor-selective ligands on proliferation of prostate cancer cells.
AU de Vos S; Dawson M I; Holden S; Le T; Wang A; Cho S K; Chen D L; Koeffler H P
CS Division of Hemotology/Oncology, UCLA School of Medicine 90048, USA.
NC CA-26038 (NCI)
CA-42710 (NCI)
CA-43277 (NCI)
+
SO Prostate, (1997 Jul 1) 32 (2) 115-21.
Journal code: 8101368. ISSN: 0270-4137.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199708
ED Entered STN: 19970813
Last Updated on STN: 19970813
Entered Medline: 19970804
AB BACKGROUND: Management of prostate cancer that either is detectable by prostate specific antigen (PSA) measurements after curative intent or has

spread outside of its capsule is a serious problem. Innovative, nontoxic approaches to the disease are required. One approach might be therapy with **retinoids.** **Retinoid** activities are mediated by two distinct families of transcription factors: the **retinoic** acid receptors (RARs) and **retinoid** X receptors (RXRs), which can induce transcriptional activation through specific DNA sites or by inhibiting the transcription factor AP-1 that usually mediates cellular proliferative signals. The RARs require heterodimerization with RXRs. RXRs can form either heterodimers or homodimers; and the latter can bind to DNA response elements that are distinct from those bound by the **RAR**/RXR heterodimers. METHODS: A series of novel synthetic **retinoids** that selectively interact with RXR/RXR homodimers or **RAR**/RXR heterodimers, or that selectively inhibit AP-1 activity without activating transcription were evaluated for their ability to inhibit clonal growth of three human prostate cancer cell lines (PC-3, DU-145, and LNCaP). RESULTS: Several notable findings were: 1) RXR-selective **retinoids**, such as SR11246, were able to inhibit the clonal growth of prostate cancer cells. In contrast, SR11246 had little effect on clonal growth of myeloid leukemic cells. 2) **RAR** -selective **retinoids** also inhibited clonal growth of prostate cancer cells. 3) The **retinoid** (SR11238) with potent anti-AP-1 activity had no effect on the clonal growth of prostate cancer cells. CONCLUSIONS: This study shows that both RXR- and **RAR**-selective **retinoids** are worthy of further study and may be candidates for future clinical trials in prostate cancer.

L15 ANSWER 16 OF 26 MEDLINE on STN
AN 97238885 MEDLINE
DN PubMed ID: 9083083
TI **Retinoic** acid receptor/**retinoid** X receptor heterodimers can be activated through both subunits providing a basis for synergistic transactivation and cellular differentiation.
AU Botling J; Castro D S; Oberg F; Nilsson K; Perlmann T
CS Laboratory of Tumor Biology, Department of Pathology, Uppsala University, S-751 85 Uppsala, Sweden.
SO Journal of biological chemistry, (1997 Apr 4) 272 (14) 9443-9.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199705
ED Entered STN: 19970514
Last Updated on STN: 19970514
Entered Medline: 19970508
AB The receptor for 9-cis-**retinoic** acid, **retinoid** X receptor (RXR), forms heterodimers with several nuclear receptors, including the receptor for all-trans-**retinoic** acid, **RAR** . Previous studies have shown that **retinoic** acid receptor can be activated in **RAR**/RXR heterodimers, whereas RXR is believed to be a silent co-factor. In this report we show that efficient growth arrest and differentiation of the human monocytic cell line U-937 require activation of both **RAR** and RXR. Also, we demonstrate that the allosteric inhibition of RXR is not obligatory and that RXR can be activated in the **RAR**/RXR heterodimer in the presence of **RAR** ligands. Remarkably, RXR inhibition by **RAR** can also be relieved by an **RAR antagonist.** Moreover, the dose response of RXR agonists differ between RXR homodimers and **RAR** /RXR heterodimers, indicating that these complexes are pharmacologically distinct. Finally, the AF2 activation domain of both subunits contribute to activation even if only one of the receptors is associated with ligand. Our data emphasize the importance of signaling through both subunits of a heterodimer in the physiological response to **retinoids** and show that the activity of RXR is dependent on both the identity and the ligand binding state of its partner.

L15 ANSWER 17 OF 26 MEDLINE on STN
AN 97146372 MEDLINE
DN PubMed ID: 8993231
TI **Retinoid antagonists.**
AU Umemiya H; Kagechika H; Fukasawa H; Hashimoto Y; Shudo K
CS Faculty of Pharmaceutical Sciences, University of Tokyo, Japan.
SO Yakugaku zasshi. Journal of the Pharmaceutical Society of Japan, (1996 Dec) 116 (12) 928-41. Ref: 31
Journal code: 0413613. ISSN: 0031-6903.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

10676089

(REVIEW, TUTORIAL)
LA Japanese
FS Priority Journals
EM 199703
ED Entered STN: 19970313
Last Updated on STN: 19970313
Entered Medline: 19970305
AB **Retinoids**, **retinoic** acid and its bioisosters, regulate many biological functions such as cell differentiation, proliferation and embryonic development in vertebrates, through binding to and activating their specific nuclear receptors. There are two classes of nuclear receptors for **retinoids**, **retinoic** acid receptors (**RAR** alpha, beta, gamma) and **retinoid** X receptors (RXR alpha, beta, gamma). Several **retinoid antagonists**, which bind to but not activate RARs, have been reported. Among them, 4-(5H-7,8,9,10-tetrahydro-5,7,7,10,10-pentamethylbenzo[e]naphtho [2,3-b][1,4]diazepin-13-yl)benzoic acid (LE135, 20) is a **RAR** beta-selective **retinoid antagonist**. **Structure -activity** relationships of LE135 (20) showed that the naphthalenyl analogs [LE540 (21) and LE550 (22)] are more potent **retinoid antagonists** in HL-60 assay. Contrary to the **antagonistic** activity of LE135 (20), an isomer of LE135 (20), 4-[5H-2,3-(2,5-dimethyl-2,5-hexano)-5-methyldibenzo- [b,e][1,4]diazepin-11-yl)benzoic acid (HX600, 39) enhanced the activities of **retinoids** . Although the synergistic activity of HX600 (39) can be explained by the binding to RXRs and the further activation of **RAR**/RXR heterodimer activated by **retinoid** (**RAR** ligand), the significantly different biological character of HX600 (39) from the typical RXR-selective ligand suggested the possibility of the participation of other nuclear receptors or cofactors in the **retinoid** synergism.

L15 ANSWER 18 OF 26 MEDLINE on STN
AN 96216111 MEDLINE
DN PubMed ID: 8662628
TI A novel class of **retinoid antagonists** and their mechanism of action.
AU Lee M O; Dawson M I; Picard N; Hobbs P D; Pfahl M
CS Sidney Kimmel Cancer Center, La Jolla, California 92037, USA.
SO Journal of biological chemistry, (1996 May 17) 271 (20) 11897-903.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 199608
ED Entered STN: 19960911
Last Updated on STN: 19970203
Entered Medline: 19960829
AB **Retinoids** regulate a broad range of biological processes through two subfamilies of nuclear **retinoid** receptors, the **retinoic** acid receptors (RARs) and the **retinoid** X receptors (RXRs). Recently, we reported a novel type of **retinoic** acid **antagonist** (SR11335) and showed that this compound can inhibit **retinoic** acid (RA)-induced activation of a human immunodeficiency virus type 1 (HIV-1) promoter construct that contains a special RA response element (RARE). We have now further characterized the antagonism mediated by SR11335 and of newly synthesized structurally related compounds. Two compounds, SR11330 and SR11334, which are poor transactivators, also showed **antagonist** activities, inhibiting all-trans-RA (tRA) and 9-cis-RA. The **retinoids** inhibited transcriptional activation of **RAR**/RXR heterodimers effectively, while inhibition of RXR homodimers was less efficient. Inhibition was observed on several RAREs, including the TREpal, betaRARE, apoAI-RARE, and CRBPI-RARE. In addition, the **antagonists** inhibited tRA-induced differentiation of HL-60 cells. The **antagonist** did not interfere with DNA binding of the receptors. In limited proteolytic digestion assays, SR11335 induced resistance of the receptors to proteolysis, but the pattern of the degradation was not altered from that induced by tRA, suggesting that these **antagonists** induce their biological effects by competing with agonists for binding to RARs, thereby preventing the induction of conformational changes of the receptors necessary for transcriptional activation.

L15 ANSWER 19 OF 26 MEDLINE on STN
AN 96130346 MEDLINE
DN PubMed ID: 8544175
TI Synthesis, structure-affinity relationships, and biological activities of

10676089

ligands binding to **retinoic** acid receptor subtypes.
AU Charpentier B; Bernardon J M; Eustache J; Millois C; Martin B; Michel S; Shroot B
CS CIRD GALDERMA, Sophia Antipolis, Valbonne, France.
SO Journal of medicinal chemistry, (1995 Dec 22) 38 (26) 4993-5006.
Journal code: 9716531. ISSN: 0022-2623.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199602
ED Entered STN: 19960227
Last Updated on STN: 19970203
Entered Medline: 19960213
AB The **retinoic** acid receptors (RARs) transduce **retinoid** dependant gene regulation, and many biological effects of **retinoids** are mediated through binding and activation of three closely related receptor subtypes (**RAR** alpha, **RAR** beta, and **RAR** gamma). In order to investigate the role of receptor subtypes, we have carried out a chemical synthesis program to seek selective **retinoids** for these receptors. We measured receptor binding affinity using recombinant **RAR** alpha, -beta, and -gamma proteins and assessed cellular differentiating activity in F9 murine teratocarcinoma cells (F9 cells). This research has identified the 4-substituted-3-(1-adamantyl)phenyl moiety as a new pharmacophore which can replace the beta-cyclogeranylidene ring of the naturally occurring all-trans-**retinoic** acid. Two chemical series derived from the general structures 6-(3-tertioalkylphenyl)-2-naphthoic acid (series I) and 4-[(E)-2-(3-tertioalkylphenyl)propenyl]benzoic acid (series II) were developed. In particular, we have obtained the **RAR** gamma selective derivatives 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthoic acid (7) [Ki(**RAR** alpha) = 6500 nM, Ki(**RAR** beta) = 2480 nM, Ki(**RAR** gamma) = 77 nM] and 4-[(E)-2-[3-(1-adamantyl)-4-hydroxyphenyl]propenyl]benzoic acid (19) [Ki(**RAR** alpha) = 1,144 nM, Ki(**RAR** beta) = 1245 nM, Ki(**RAR** gamma) = 53 nM]. In series I, the presence of a phenol group, irrespective of the nature of tertioalkyl group, imparted at least partial **RAR** gamma selectivity, whereas in series II, the presence of both adamantyl and phenol groups is needed to confer **RAR** gamma selectivity. The **RAR** gamma selective ligands induce differentiation in F9 cells (7, AC50 = 33 nM; 19, AC50 = 66 nM). From series I, a mixed **RAR** beta-gamma agonist with potent cellular differentiating activity was selected for development as a topical antiacne agent, 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid (5, CD 271) [Ki(**RAR** alpha) = 1100 nM, Ki-(**RAR** beta) = 34 nM, Ki(**RAR** gamma) = 130 nM, AC50(F9) = 37 nM]. Finally, from series II, we have obtained a weak **antagonist** in the F9 cellular differentiation assay, 4-[(E)-2-(3-tert-butyl-4-hydroxyphenyl)propenyl]benzoic acid (15, IC50 = 700 nM).

L15 ANSWER 20 OF 26 MEDLINE on STN
AN 96125026 MEDLINE
DN PubMed ID: 8547646
TI Myeloid differentiation and **retinoblastoma** phosphorylation changes in HL-60 cells induced by **retinoic** acid receptor- and **retinoid** X receptor-selective **retinoic** acid analogs.
AU Brooks S C 3rd; Kazmer S; Levin A A; Yen A
CS Department of Pathology, Cornell University, Ithaca, NY 14853, USA.
NC ES 07052 (NIEHS)
SO Blood, (1996 Jan 1) 87 (1) 227-37.
Journal code: 7603509. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199602
ED Entered STN: 19960306
Last Updated on STN: 19970203
Entered Medline: 19960216
AB The ability of subtypes of **retinoic** acid receptors (RARs) and **retinoid** X receptors (RXRs) singly and in combination to elicit myeloid differentiation, G1/0-specific growth arrest, and **retinoblastoma** (RB) tumor suppressor protein dephosphorylation was determined in the human myeloblastic leukemia cell line HL-60 using subtype-selective **retinoic** acid (RA) analogs. RA analogs that selectively bind only to RARs (Am580 and/or TTNPB) or to RXRs (Ro 25-6603, SR11237, and/or SR11234) did not elicit the above-mentioned three cellular responses. In contrast, simultaneous treatment with both an **RAR**

-selective ligand (Am580 or TTNPB) and an RXR-selective ligand (Ro 25-6603, SR11237, or SR11234) induced all three cellular processes. An **RAR** alpha-selective ligand used with an RXR-selective ligand generated the same responses as did all-trans RA or 9-cis RA, which affect both families of receptors, suggesting an important role for **RAR** alpha among **RAR** subtypes in eliciting cellular response. Consistent with this finding, the **RAR** alpha **antagonist**, Ro 41-5253, reduced the level of the cellular responses elicited by treatment with an **RAR** alpha-selective ligand plus RXR-selective ligand. The coupling of the shift of RB to its hypophosphorylated form with G1/0 arrest and differentiation in response to ligands is consistent with a possible role of RB as a downstream target or effector of **RAR** alpha and RXR in combination.

L15 ANSWER 21 OF 26 MEDLINE on STN
AN 96107242 MEDLINE
DN PubMed ID: 8530518
TI Enhancement of HL-60 differentiation by a new class of **retinoids** with selective activity on **retinoid** X receptor.
AU Apfel C M; Kamber M; Klaus M; Mohr P; Keidel S; LeMotte P K
CS Department of Dermatology, F. Hoffmann-LaRoche, Basel, Switzerland.
SO Journal of biological chemistry, (1995 Dec 22) 270 (51) 30765-72.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199601
ED Entered STN: 19960220
Last Updated on STN: 19970203
Entered Medline: 19960130
AB Cellular responsiveness to **retinoic** acid and its metabolites is conferred through two distinct families of receptors: the **retinoic** acid receptors (RARs) and the **retinoid** X receptors (RXRs). Herein, we report on the identification and characterization of several conformationally restricted **retinoids**, which selectively bind and activate RX receptors. Under the influence of **retinoids**, HL-60 myelocytic leukemia cells differentiate into granulocytes. This effect is mediated by **RAR** alpha, as has been demonstrated through the use of a selective **RAR** alpha **antagonist** (Apfel, C., Bauer, F., Crettaz, M., Forni, L., Kamber, M., Kaufmann, F., LeMotte, P., Pirson, W., and Klaus, M. (1992) Proc. Natl. Acad. Sci. U.S.A. 89, 7129-7133). Here, we show that conformationally restricted RXR-specific **retinoids**, at doses that are per se inactive, are able to potentiate by up to one order of magnitude the pro-differentiating effects of all-trans **retinoic** acid and an **RAR** alpha-selective synthetic **retinoid.** We also present evidence that these RXR-selective ligands are able to bind to a DNA RXR.**RAR** heterodimer complex. This finding demonstrates that agonists for RARs and RXRs can synergistically promote HL-60 differentiation, which could be mediated through a heterodimer of these receptors.

L15 ANSWER 22 OF 26 MEDLINE on STN
AN 95401217 MEDLINE
DN PubMed ID: 7671258
TI Correlation of **retinoid** binding affinity to **retinoic** acid receptor alpha with **retinoid** inhibition of growth of estrogen receptor-positive MCF-7 mammary carcinoma cells.
AU Dawson M I; Chao W R; Pine P; Jong L; Hobbs P D; Rudd C K; Quick T C; Niles R M; Zhang X K; Lombardo A; +
CS Life Sciences Division, SRI International, Menlo Park, California 94025, USA.
NC 1 P01 CA51993 (NCI)
1 R01 CA63335 (NCI)
SO Cancer research, (1995 Oct 1) 55 (19) 4446-51.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199510
ED Entered STN: 19951026
Last Updated on STN: 19970203
Entered Medline: 19951019
AB Both anchorage-dependent growth and anchorage-independent growth of the estrogen receptor-positive mammary carcinoma cell line MCF-7 are inhibited by all-trans-**retinoic** acid. This cell line has nuclear **retinoic** acid receptors (RARs) alpha and gamma. The natural

retinoids all-trans-**retinoic** acid and 9-cis-**retinoic** acid and a series of 12 conformationally restricted **retinoids**, which showed a range of binding selectivities for these receptors and had either agonist or **antagonist** activity for gene transcriptional activation by the RARs, were evaluated for their abilities to inhibit anchorage-dependent (adherent) and anchorage-independent (clonal) growth of MCF-7 cells. Correlation analyses were performed to relate growth inhibition by these **retinoids** with their binding affinity to **RAR** alpha or **RAR** gamma. Inhibition of anchorage-dependent growth in culture after 7 days of **retinoid** treatment correlated with binding to **RAR** alpha (n = 14; P < or = 0.001) and not to **RAR** gamma (n = 14; P > 0.1). Both the **RAR** alpha-selective **retinoid** agonists and the two **RAR antagonists** that were evaluated inhibited adherent cell growth. The **RAR** gamma-selective agonists had very low growth inhibitory activity (< 10%) at concentrations as high as 12.5 microM. These results suggest that **RAR** alpha is the **retinoid** receptor involved in the inhibition of adherent cell growth by **retinoids** and that transcriptional activation by this receptor on a **RAR** response element does not appear to be required for this process to occur. For this series of **retinoids**, inhibition of anchorage-independent growth after 21 days of **retinoid** treatment only correlated (n = 12; P < or = 0.005) with binding affinity to **RAR** alpha for the **retinoid** agonists, although the **RAR** gamma-selective **retinoids** displayed weak activity. The **RAR antagonists** were very poor inhibitors of growth. These results suggest that activation of gene transcription by **RAR** alpha appears to be required for inhibition of anchorage-independent growth by **retinoids** in this estrogen receptor-positive mammary carcinoma cell line.

L15 ANSWER 23 OF 26 MEDLINE on STN
AN 95156220 MEDLINE
DN PubMed ID: 7853147
TI Novel synthetic **retinoid** agonists and **antagonists.**
AU Kagechika H
CS Faculty of Pharmaceutical Sciences, University of Tokyo, Japan.
SO Yakugaku zasshi. Journal of the Pharmaceutical Society of Japan, (1994 Nov) 114 (11) 847-62. Ref: 45
Journal code: 0413613. ISSN: 0031-6903.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA Japanese
FS Priority Journals
EM 199503
ED Entered STN: 19950322
Last Updated on STN: 19950322
Entered Medline: 19950313
AB **Retinoic** acid acts as a specific modulator of cellular differentiation and proliferation. Its natural and synthetic analogs, classified as **retinoids**, can be applied to the chemotherapy in the field of dermatology and oncology. Various benzoic acid derivatives exhibited the specific biological responses of **retinoic** acid and were named **retinobenzoic** acids. Especially, the aromatic amides such as Am80 and Am580 have better therapeutic effects than **retinoic** acid. N-Methylation of these highly active aromatic secondary amides caused the disappearance of the activity due to the change of the amide conformation from trans into cis. From such observations, the conformation of the linking group between alkyl-substituted benzene ring and benzoic acid moiety is an important factor for the activity. Some **retinobenzoic** acids do not bind to the cellular-**retinoic** acid-binding protein, but bind to nuclear **retinoic** acid receptors (RARs) with the binding affinity corresponding to the potency of their biological activities. Among them, Am80 can bind to two of the three **RAR** subtypes (**RAR** alpha and beta). The selectivity is favorable for the clinical application of **retinoid** since it has possibility to elicit a part of a number of the biological activities of **retinoic** acid.

L15 ANSWER 24 OF 26 MEDLINE on STN
AN 94006199 MEDLINE
DN PubMed ID: 8402597
TI Correlation of the ability of **retinoids** to inhibit promoter-induced anchorage-independent growth of JB6 mouse epidermal cells with their activation of **retinoic** acid receptor gamma.
AU Rudd C J; Mansbridge J N; Suing K D; Dawson M I

10676089

CS Life Sciences Division, SRI International, Menlo Park, California 94025.
NC 5 P01 CA51993 (NCI)
SO Cancer letters, (1993 Sep 15) 73 (1) 41-9.
Journal code: 7600053. ISSN: 0304-3835.
CY Ireland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199311
ED Entered STN: 19940117
Last Updated on STN: 19940117
Entered Medline: 19931102
AB **Retinoids** inhibit the biological effects induced in mouse epidermal cells by the tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA). Specific nuclear **retinoic** acid receptors (RARs) have been identified in the epidermis, but the specific receptor that mediates the inhibitory response by **retinoids** is not established. **Retinoic** acid and six conformationally restricted **retinoids** were evaluated in an in vitro bioassay using the JB6 mouse epidermal cell line. These activities were then compared with the ability of these **retinoids** to activate the RARs in transient transfection assays for transcriptional activation to identify the **retinoid** receptor involved in inhibiting TPA-induced anchorage-independent growth. The **retinoids** inhibited TPA-induced colony formation of JB6 cells in semisolid medium at concentrations that were not toxic based on colony formation of attached cells. These concentrations ranged from less than 10(-9)-10(-6) M. 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylanthracen-2-yl)benzoic acid (TTAB) was the most potent **retinoid**, with an EC50 of 0.8 nM. Both **RAR** alpha and **RAR** gamma were expressed in JB6 cells. Expression of **RAR** beta was not detected in these cells using a polymerase chain reaction assay, consistent with its extremely low level in mouse skin. Inhibition of the TPA response by these **retinoids** in JB6 cells correlated only with their transcriptional activation of **RAR** alpha, but not with that of **RAR** alpha. These results suggest that **RAR** gamma is most probably the receptor that mediates the chemopreventive effects of **retinoids** in mouse epidermis.

L15 ANSWER 25 OF 26 MEDLINE on STN
AN 92357785 MEDLINE
DN PubMed ID: 1323127
TI A **retinoic** acid receptor alpha **antagonist** selectively counteracts **retinoic** acid effects.
AU Apfel C; Bauer F; Crettaz M; Forni L; Kamber M; Kaufmann F; LeMotte P; Pirson W; Klaus M
CS Pharma Division, Preclinical Research, F. Hoffmann-La Roche, Basel, Switzerland.
SO Proceedings of the National Academy of Sciences of the United States of America, (1992 Aug 1) 89 (15) 7129-33.
Journal code: 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199209
ED Entered STN: 19920925
Last Updated on STN: 19970203
Entered Medline: 19920904
AB **Retinoic** acid (RA) exerts its pleiotropic effects on cell growth and differentiation through the activation of a family of transcription factors-the RA receptors (RARs). Three subtypes of these receptors exist, **RAR** alpha, **RAR** beta, and **RAR** gamma. The receptors are differentially expressed in different cell types and stages of development, suggesting that they may regulate different sets of genes. We have identified a synthetic **retinoid** with the characteristics of a selective **RAR** alpha **antagonist**. This **antagonist** counteracts RA effects on HL-60 cell differentiation and on B-lymphocyte polyclonal activation. Beyond its potential practical relevance, this and other specific **antagonists** will be useful to dissect the **RAR** system and to assign to one given receptor each of the many RA-regulated functions.

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TI **Retinoids** and their nuclear receptors.
AU Hashimoto Y; Shudo K

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AB **Retinoids** (**retinoic** acid and its biofunctional analogs) are widely involved in the control of cell proliferation, cell differentiation, and embryogenic development. A series of novel synthetic **retinoids** (called **retinobenzoic** acids), which include **retinoid antagonists**, have been developed and have been shown to be useful tools to investigate **retinoidal** action molecular mechanisms. **Retinoids** elicit their biological effects by binding to specific nuclear receptors (RARs) belonging to a steroid/thyroid nuclear receptor superfamily. RARs act as **retinoid**-dependent transcription factors which bind to a specific gene site and control the gene's expression. The diversity of **retinoidal** actions can possibly be interpreted by considering the following characteristics, all of which are quite diversified: the structure and spatial/temporal distribution of RARs, the base sequences which interact with RARs, the cell type specifically determined hierarchy of gene expression, and the nuclear coregulators which interact with RARs. Abnormality of an **RAR** gene which might cause acute promyelocytic leukemia is also discussed.